1 FINAL CLINICAL STUDY PROTOCOL

Lumosa Therapeutics Co, Ltd

Protocol Title: A Phase IIa, Double-Blind, Single Dose, Randomized, Placebo-Controlled Study to Evaluate the Safety, Tolerability, and Potential Efficacy of LT3001 Drug Product in Subjects with Acute Ischemic Stroke (AIS)

Protocol Number: LT3001-201

[redacted]

[redacted]

Name of Investigational Product:	LT3001 drug product
Phase of Development:	IIa
Indication:	Acute Ischemic Stroke (AIS)
Sponsor:	Lumosa Therapeutics 4th Floor, No. 3-2, Park Street, Nangang District, Taipei, 11503, Taiwan Tel: +886-2-26557918 Fax: +886-2-26557919
Protocol Version:	Version 2.1
Protocol Date:	Final 17 February 2020

PROTOCOL APPROVAL SIGNATURES

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This study will be conducted in compliance with the clinical study protocol (and amendments), International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines for current Good Clinical Practice (GCP)/ISO14155 (Clinical Investigation for Medical Devices for Human Subjects–Good Clinical Practice)/International Society for Pharmacoepidemiology (ISPE) Guidelines for Good Pharmacoepidemiology Practices (GPP), and applicable regulatory requirements.

[redacted]

INVESTIGATOR SIGNATURE PAGE

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Confidentiality and Current Good Clinical Practice (GCP)/E6(R2) Compliance Statement

- I, the undersigned, have reviewed this protocol, including appendices, and I will conduct the study as described in compliance with this protocol (and amendments), GCP, and relevant International Council for Harmonisation (ICH) guidelines.
- I am thoroughly familiar with the appropriate use of the investigational product, as described in this protocol and any other information provided by Lumosa Therapeutics including, but not limited to, the current investigator's brochure (IB).
- Once the protocol has been approved by the independent ethics committee (IEC)/institutional review board (IRB), I will not modify this protocol without obtaining prior approval of Lumosa Therapeutics and of the IEC/IRB. I will submit the protocol amendments and/or any informed consent form modifications to Lumosa Therapeutics and the IEC/IRB, and approval will be obtained before any amendments are implemented.
- I ensure that all persons or party assisting me with the study are adequately qualified and informed about the Lumosa Therapeutics investigational product and of their delegated study-related duties and functions as described in the protocol.
- I ensure that source documents and trial records that include all pertinent observations on each of the site's trial subjects will be attributable, legible, contemporaneous, original, accurate, and complete.
- I understand that all information obtained during the conduct of the study with regard to the subjects' state of health will be regarded as confidential. No subjects' names will be disclosed. All subjects will be identified by assigned numbers on all case report forms, laboratory samples, or source documents forwarded to the Sponsor. Clinical information may be reviewed by the Sponsor or its agents or regulatory agencies. Agreement must be obtained from the subject before disclosure of /subject information to a third party.
- Information developed in this clinical study may be disclosed by Lumosa Therapeutics to other clinical Investigators, regulatory agencies, or other health authority or government agencies as required.

[redacted]

2 SYNOPSIS

Title of Study:	A Phase IIa, Double-Blind, Single Dose, Randomized, Placebo-Controlled Study to Evaluate the Safety, Tolerability, and Potential Efficacy of LT3001 Drug Product in Subjects with Acute Ischemic Stroke (AIS)
Protocol Number:	LT3001-201
Investigators/Study Sites:	The study is planned to take place in [redacted] in Taiwan and the United States (US).
Phase of Development:	Phase IIa
Objectives:	Primary Objective: To determine the safety of a single dose [redacted] of LT3001 drug product administered intravenously (IV) in subjects with acute ischemic stroke (AIS). Secondary Objectives: a) To determine the tolerability of a single dose [redacted] of LT3001 drug product administered IV in subjects with AIS. b) To determine the potential efficacy of a single dose [redacted] of LT3001 drug product administered IV in subjects with AIS. [redacted]
Study Endpoints:	Primary endpoint: The occurrence of symptomatic intracranial hemorrhage (sICH) within 36 hours after dosing; clinical deterioration defined as an increase in the National Institute of Health Stroke Scale (NIHSS) of 4 points or more AND confirmed by computed tomography (CT)- or magnetic resonance imaging (MRI)-documented. Secondary endpoints: a) The occurrence of sICH [redacted]. b) The occurrence of asymptomatic intracranial hemorrhage (ICH) [redacted]. c) The occurrence of mortality due to intracerebral or other major bleeding complications [redacted]. d) The occurrence of mortality due to any reason [redacted]. e) Number and severity of adverse events (AEs) [redacted]. f) The number of subjects with AEs [redacted]. g) The occurrence of recurrent stroke [redacted]. h) Functional outcome • The frequency and percentage of subjects with each grade on modified Rankin Scale (mRS) [redacted]. • The frequency and percentage of subjects with mRS≤2 [redacted]. i) Neurological outcome • Absolute change in NIHSS [redacted]. • The proportion of subjects with NIHSS ≤2 [redacted]

	[redacted]
Study Design:	This is a multicenter, double-blind, single-dose, randomized, and placebo-controlled prospective Phase IIa clinical study, designed to evaluate LT3001 drug product versus placebo/control in subjects with AIS. Approximately 24 eligible subjects will be randomized 2:1 to LT3001 drug product or placebo. Each eligible subject will receive a single dose [redacted] of LT3001 drug product or placebo within 24 hours after stroke symptoms onset. LT3001 drug product or placebo will be administered via a [redacted] IV infusion. The infusion will be stopped if a serious adverse event (SAE) occurs during infusion. [redacted] The participation for each subject is approximately 92 days from the screening visit (Visit 1) to the last visit.
Selection of Subjects:	Main Inclusion Criteria: Subjects a) are to be aged 18 to 90 years, inclusive, at the time of Screening (Visit 1), b) have a NIHSS of 4 to 30, c) clinical diagnosis of AIS within 24 hours after stroke symptoms onset, [redacted] e) and are able to receive the investigational product within 24 hours after stroke symptoms onset. Subjects who are women of childbearing potential (WOCBP) or are men whose sexual partners are WOCBP are to use a highly effective method of contraception during the study until 3 months after dosing of the investigational product. All subjects are to provide their signatures on the informed consent form (ICF) after receiving full information about the study. In the event the subject is unable to sign, his/her legal representative may sign on his/her behalf. Main Exclusion Criteria: Subjects who meet any of the following will be excluded: a) Treatment with recombinant tissue-type plasminogen activator (rtPA) and/or endovascular thrombectomy during the current AIS; b) presence of a pre-stroke disability where subject requires help for activities of daily living [redacted]; c) imaging evidence of acute intracranial hemorrhage, intraparenchymal tumor, arteriovenous malformations, other central nervous system lesions that could increase bleeding risk, or aneurysm requiring treatment; [redacted] e) presence of symptoms of suspected subarachnoid hemorrhage [redacted]; f) generalized seizure [redacted]; g) current uncontrolled hypertension [redacted]

	[redacted] h) International Normalized Ratio (INR) >1.7 and/or abnormal activated partial thromboplastin time (aPTT) or platelet count <100,000/mm^3; i) blood glucose concentration <50 mg/dL or >400 mg/dL; j) lactating or pregnant subjects or those planning to become pregnant during the study (pregnancy test required for all female subjects); k) received anticoagulants and/or oral dual antiplatelet therapy and glycoprotein IIb/IIIa inhibitors within 48 hours prior to treatment; l) any of the following within 90 days of Screening (Visit 1) - prior AIS, myocardial infarction, serious head trauma, history of ICH, or major surgery; m) bleeding event within 21 days of Screening (Visit 1); n) puncture of noncompressible vessels within 7 days of Screening (Visit 1); and o) severe hepatic, renal, and/or infectious disease at Screening (Visit 1).
Planned Sample Size:	Approximately 24 eligible subjects will be randomized 2:1 to LT3001 drug product or placebo.
Investigational Therapy:	LT3001 drug product [redacted]
Reference Therapy:	Placebo [redacted]
Treatment Duration:	All subjects will receive a single dose of investigational product on Day 0. The participation for each subject is approximately 92 days from the screening visit [redacted] to the last visit. The whole study is expected to last for approximately 12 months (first subject first visit [FSFV] to last subject last visit [LSLV]).
Safety:	The primary safety endpoint is the occurrence of sICH within 36 hours after dosing and will be assessed via NIHSS and imaging (CT or MRI). [redacted] Additional evaluations include the occurrence of asymptomatic ICH, mortality due to intracerebral or other major bleeding complications, mortality due to any reason, and the incidence of AEs, including the relationship to study treatment and severity.
Efficacy:	Functional outcome will be assessed using the mRS and neurological outcome will be assessed using the NIHSS [redacted] The occurrence of recurrent stroke [redacted]
[redacted]	[redacted]
Statistical Methods and Planned Analyses:	<u>Study populations</u> • Enrolled Population: all individuals who sign the informed consent form. • Intent-to-Treat (ITT) Population: all subjects who are randomized, irrespective of any deviation from the protocol or premature discontinuation. The treatment group assignment will be designated according to initial randomization. The ITT population will serve as the primary basis for the analysis of efficacy. • [redacted]

- Per-Protocol (PP) Population: all ITT subjects who complete study procedures through Day 90 without a major protocol deviation. The PP population will also be used for analysis of efficacy.
- [redacted]
- Safety Population: all randomized subjects who receive at least 1 dose of investigational product. The treatment group assignment in this population will be defined by the treatment actually received. This population will be used for the analysis of safety.

Safety analyses

The frequency and proportion of sICH and asymptomatic ICH at the different timepoints of interest noted in the Study Endpoints section above [redacted] will be reported by treatment group and overall. [redacted]

For the occurrence of mortality (due to intracerebral or other major bleeding complications or due to any reason), analyses will be similar to that noted above for frequency and proportion of sICH and asymptomatic ICH: comparisons by treatment group made using [redacted]. The overall proportion of subjects with an increase in the NIHSS of ≥4 points will also be presented by treatment group.

The incidence of AE [redacted] will be reported by treatment group and overall using descriptive statistics noting the frequency and proportion of subjects. No formal statistical tests will be done.

Efficacy analyses

The occurrence of recurrent stroke [redacted] will be summarized using descriptive statistics noting the frequency and proportion of subjects who meet this endpoint.

[redacted]

The total score and absolute change from Baseline for NIHSS will be summarized and the proportion of subjects with NIHSS of 0-2 points will be presented by treatment group. The frequency and percentage of subjects with each grade on the mRS and who achieve a score of 0-2 will be presented by treatment group [redacted]
No formal adjustment for multiple comparisons will be made.

Shift analysis of scores for mRS will be provided using descriptive statistics noting the frequency and proportion of subjects. No formal statistical tests will be done.

[redacted]

3 TABLE OF CONTENTS

[redacted]

3.1 List of In-text Tables

3.2 List of In-text Figures

4 LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
AIS	acute ischemic stroke
aPTT	activated partial thromboplastin time
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
CI	confidence interval
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
ECG	electrocardiogram
EDC	electronic data capture
eCRF	electronic case report form
FDA	Food and Drug Administration
FIH	first-in-human
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
[redacted]	[redacted]
HIPAA	Health Insurance Portability Accountability Act
[redacted]	[redacted]
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation OR intracranial hemorrhage
[redacted]	[redacted]
IEC	independent ethics committee
INR	International Normalized Ratio
IRB	institutional review board
ITT	intent-to-treat
IV	intravenous
[redacted]	[redacted]
mRS	modified Rankin Scale
[redacted]	[redacted]
NIHSS	National Institute of Health Stroke Scale
PK	pharmacokinetic
PP	Per-Protocol
PT	prothrombin time

Abbreviation	Definition
rtPA	recombinant tissue-type plasminogen activator
[redacted]	[redacted]
SAE	serious adverse event
sICH	symptomatic intracranial hemorrhage
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
WOCBP	women of childbearing potential
US	United States

5 INTRODUCTION

5.1 General Information on Acute Ischemic Stroke

Stroke is classically characterized as a neurological deficit attributed to an acute focal injury of the central nervous system by a vascular cause.[1] Ischemic strokes account for about 87% of all strokes; 10% are intracerebral hemorrhage strokes, whereas 3% are subarachnoid hemorrhage strokes.[2] Annually, 15 million people worldwide suffer a stroke; in the United States (US), on average, someone experiences stroke every 40 seconds.[2,3] Globally, stroke is the second leading cause of death above the age of 60 years and is the leading cause of disability.[4,5]

The ultimate result of ischemic cascade initiated by acute stroke is neuronal death along with an irreversible loss of neuronal function via direct starvation from lack of glucose, failure of adenosine triphosphate production, membrane depolarization, rise in intracellular calcium, and free radical production.[5,6] Furthermore, free radicals directly damage cells and also initiate other reactions that lead to cerebral edema.[7] Based on the pathogenesis of ischemic stroke, the 2 main aims of the treatment strategies in ischemic stroke are restoration of cerebral blood flow and reduction of the harmful effects of ischemia on neurons.[5]

Alteplase (Activase®), a recombinant tissue-type plasminogen activator (rtPA), was the first medication approved for the treatment of ischemic stroke by the US Food and Drug Administration (FDA) in 1996 (BLA 103172/S-1055). Although alteplase has been shown to improve the outcome of subjects with acute ischemic stroke (AIS), its use has been limited due to the low eligibility rate for this medication. The most common exclusion for alteplase is the delay in seeking medical attention; only 22% to 31% of patients with ischemic stroke present to an emergency department within the time window approved for rtPA administration, which is 3 or 4.5 hours after symptom onset.[8] In addition, symptomatic intracerebral hemorrhage is the most feared complication after intravenous (IV) alteplase; with nearly 5-fold risk even when alteplase was given within 3 hours, as shown in a recent meta-analysis of 1779 subjects.[8] The time window allowed for rtPA treatment varies among countries; for example, FDA did not approve the change from 3 hours to 4.5 hours after their review of the trial results and unpublished data from alteplase manufacturer.[8] Administration later than 4.5 hours is associated with an increased risk of mortality, and the risk-benefit ratio has not been established (SIGN 2008).[9]

Restoration of the blood supply is essential to minimize the damage caused by the ischemic condition, but reperfusion by thrombolytic drugs such as alteplase and angioplasty techniques often lead to an increase in the extent of brain injury. This reperfusion injury is thought to be caused by the activity of free radicals.[10] Although the benefit of alteplase is well established, its adverse effects remain the major concerns for the use of the thrombolytic agent. Additionally, rtPA also has potential for direct neurotoxicity that is not related to its thrombolytic activity.[11]

Due to the abovementioned reasons, the usage rate of alteplase is low, with only approximately 5% of stroke patients being administered alteplase.[12] As such, there is a need to develop

treatments that can offer similar efficacy to alteplase but with a lower increase of bleeding and/or longer therapeutic window.

5.2 Background on LT3001

LT3001 [redacted] is a novel small molecule designed to have both thrombolytic and free radical scavenging activities, which were characterized in various in vitro and in vivo models. In vitro studies have shown that LT3001 exhibits substantial anti-oxidation activity. In animal studies, LT3001 can restore blood flow, reduce cerebral infarct volume, and improve neurological outcome in rodent and non-human primate stroke models, with an apparent wider therapeutic time window and a better safety profile than those reported for rtPA. Effect of LT3001 on the bleeding time was evaluated in male Institute of Cancer Research (ICR) mice using an amputation tail model. The tail bleeding time of mice treated with [redacted] LT3001 was comparable to animals that received vehicle control and significantly shorter than those treated with rtPA (10 mg/kg).

LT3001 appears to have both thrombolytic and free radical scavenging effects with minimal risk of bleeding and potentially extended treatment time window. Therefore, LT3001 is being developed for the treatment of AIS.

5.2.1 Nonclinical Studies

The nonclinical program for LT3001 included the following:

- In vitro pharmacology studies to evaluate antioxidant activity, anti-platelet activity, [redacted] and binding to receptors and critical enzymes;
- In vivo pharmacology studies to evaluate efficacy in mouse, rat, and monkey models of stroke;
- Good Laboratory Practices (GLP) safety pharmacology studies, involving neurological and respiratory in rats, cardiovascular in dogs, an in vitro human Ether-a-go-go Related Gene (hERG) assay, and a non-GLP cardiovascular study in monkeys;
- In vivo pharmacokinetic (PK)/toxicokinetic evaluations in rats, dogs, and mini-pigs;
- In vitro distribution and metabolism studies using mouse, rat, dog, monkey, mini-pig, and human hepatocytes;
- Acute toxicity studies in rats, dogs, monkeys, and mini-pigs;
- 14-day repeat-dose GLP toxicity studies in rats and dogs;
- 6-day repeat-dose GLP toxicity study in mini-pigs;
- In vitro genotoxicity studies and in vivo genotoxicity evaluation in rats; and
- In vitro phototoxicity study.

A summary of noteworthy findings from these nonclinical studies is listed below:

- Effect of LT3001 on the bleeding time was evaluated in male ICR mice and was comparable to animals that received vehicle control and significantly shorter than those treated with rtPA (10 mg/kg).
- LT3001 showed stronger antioxidant capacity than the known antioxidant control substances (Trolox®, L-ascorbic acid, and Edaravone).
- The interaction of LT3001 and Aspirin was assessed by optical microplate-based assay. LT3001 [redacted] showed no effect on Aspirin's anti-platelet aggregation activity.
- In secondary pharmacodynamic studies, LT3001, [redacted] had no effect on any of the receptors or critical enzymes evaluated.
- In GLP safety pharmacology studies in vivo, LT3001 [redacted] showed no biologically significant effect in either the central nervous system Irwin test or respiratory physiological parameters in rats.
- In a GLP [redacted] assay in vitro, [redacted] inhibition of mean hERG-mediated potassium currents was observed at the highest concentration tested [redacted] No inhibition was observed [redacted].
- In 2 GLP cardiovascular studies in dogs, a decrease in blood pressure and an increase in heart rate (with concomitant decreases in RR, PR, and uncorrected QT intervals) were observed at LT3001 [redacted]
- In a non-GLP cardiovascular study in monkeys, a decrease in blood pressure and an increase in heart rate (a compensatory response to decreased blood pressure) were observed [redacted]. The effects on cardiovascular parameters were all transient and recovered to normal range within a few hours.
- PK studies of LT3001 in rats, dogs, and mini-pigs indicated that LT3001 plasma levels increased roughly in proportion to the IV dose [redacted] with no signs of accumulation after repeated doses.
- In vitro protein binding studies showed that LT3001 does not bind significantly to human serum albumin (HSA) or serum acid alpha-1-glycoprotein (AGP), which are considered the most relevant drug carriers in human plasma. [redacted]
- In vitro metabolite identification studies with LT3001 were conducted using plasma and following in vitro incubation with hepatocytes from mice, rats, dogs, monkeys, mini-pigs, and humans. [redacted]

- LT3001 was not phototoxic and showed no genotoxic activity in either the Ames test or the chromosomal aberration assay with Chinese Hamster Ovary (CHO) cells. LT3001 did not induce micronuclei in rat bone marrow cells.
- Acute toxicity studies with LT3001 were conducted in rats, dogs, monkeys, and mini-pigs, respectively. [redacted]
- The repeat-dose toxicity of LT3001 was evaluated in a 5-day non-GLP study in dogs [redacted] 14-day GLP repeat-dose (once daily) IV toxicity studies in rats and in dogs [redacted] and a GLP repeat-dose study in Bama mini-pigs [redacted]. Notable LT3001-related findings included swelling and discoloration at the injection site on the tail and mild vocalization during dosing in rats; and prolonged capillary refill time, weak pulse, rapid respiration, recumbency, decreased activity, and skin redness in dogs. These clinical signs subsided or became absent with subsequent dosing. There was no mortality reported in either of the 14-day studies or during the dosing period in the 6-day mini-pig study ([redacted] prior to scheduled Day 14 sacrifice, due to a moribund condition). The no observed adverse effect levels (NOAELs) were determined [redacted]

5.2.2 Clinical Studies

[redacted] 12 human subjects have been exposed to LT3001 drug product [redacted] in the first-in-human (FIH) Phase 1, single ascending dose study (LT3001-101), which was conducted at 1 clinical site in the US. The objectives of the study were to evaluate the safety, tolerability, and PK of a single IV infusion of LT3001 drug product in healthy subjects. The study is now completed, and the results are used to determine the doses to be assessed for a Phase 1 multiple-ascending dose study in healthy subjects, and to determine the Recommended Phase 2 Dose of LT3001 drug product to be tested in future studies in AIS patients, including this study.

5.3 Clinical Risks/Benefits of LT3001

In the FIH study for LT3001 drug product [redacted] involving healthy human volunteers, the LT3001 drug product was safe and well tolerated [redacted]. There were no serious adverse events (SAEs) reported in either cohort. There were no adverse events (AEs) reported [redacted] one subject presented with an allergy to medical tape, one subject developed a hematoma that was acquired during IV needle removal, and one subject [redacted] developed a headache. All AEs occurred post dosing, were classified as mild in severity, and were resolved. The AE of "headache" was considered by the Investigator to be mild in intensity and possibly related to the investigational product; the other AEs were considered unrelated.

Safety data collected in this study also included vital signs (heart rate, blood pressure, respiratory rate, and body temperature), electrocardiograms (ECGs), clinical biochemistry, hematology, and coagulation/clotting parameters. There were no clinically significant findings in any of the safety parameters measured.

Based on the outcomes of this study and the nonclinical studies, the safety monitoring plan for all LT3001 clinical studies will include the following:

1. Physical examination.
2. Assessment of vital signs.
3. Monitoring of injection site reactions.
4. Clinical laboratory tests including hematology and clinical biochemistry.
5. Coagulation/clotting parameters, including prothrombin time, activated partial thromboplastin time, and thrombin time.
6. ECG monitoring (single lead).
7. Stool occult blood assessment.
8. Monitoring of AEs.

Overdose

The dose level of LT3001 drug product will be calculated by the Investigator or a qualified designee [redacted]. Since drug accumulation is not anticipated due to the short half-life of LT3001 and subjects will only receive LT3001 drug product administered by an Investigator or a qualified designee and under close monitoring, it is anticipated that the risk of overdose or medication error will be low.

Any overdose, with or without associated AEs, should be promptly reported by the Investigators or designee [redacted]. Overdoses and medication errors will be documented as protocol deviations and communicated to the Study Monitor.

No specific therapy for overdose of LT3001 drug product exists. In the event of overdose or medication error, appropriate standard of care therapy for the subject/patient's symptoms and clinical status will be provided.

Details regarding known or anticipated benefits and risks, as well as reasonably anticipated AEs for LT3001 may be found in the investigator's brochure (IB).

5.4 Study Rationale

Tissue plasminogen activator (alteplase) is the only approved drug treatment for stroke in the US and, per the labeling, must be administered within 3 hours of stroke symptom onset. The approved window of administration in some other countries is 4.5 hours of stroke symptom onset.

LT3001 is a novel chemical entity designed to have both thrombolytic and free radical scavenging activities, which were characterized in various in vitro and in vivo models. Its advantages over IV rtPA include: shorter infusion time, within 24 hours of stroke onset (as opposed to 3 hours), better recanalization rate, prevention of reperfusion injury by scavenging free radicals, no effect on bleeding time, no evidence of increase in intracranial hemorrhage (as seen with IV rtPA), and ease of use.

This Phase IIa, double-blind, single-dose, randomized, placebo-controlled study is to evaluate the safety, tolerability, and potential efficacy of LT3001 drug product in subjects/patients with AIS. The safety and potential efficacy outcomes from this Phase IIa study will guide the design of future studies in subjects/patients with AIS.

6 STUDY OBJECTIVES AND ENDPOINTS

6.1 Study Objectives

6.1.1 Primary Objective

The primary objective of the study is to determine the safety of a single dose [redacted] of LT3001 drug product administered IV in subjects with AIS.

6.1.2 Secondary Objectives

- To determine the tolerability of a single dose [redacted] of LT3001 drug product administered IV in subjects with AIS.
- To determine the potential efficacy of a single dose [redacted] of LT3001 drug product administered IV in subjects with AIS.
- [redacted]

6.2 Study Endpoints

6.2.1 Primary Endpoint

The primary endpoint of this study is the occurrence of symptomatic intracranial hemorrhage (sICH) within 36 hours after dosing -- clinical deterioration defined as an increase in the National Institute of Health Stroke Scale (NIHSS) of 4 points or more AND confirmed by computed tomography (CT)- or magnetic resonance imaging (MRI)- documented.

6.2.2 Secondary Endpoints

6.2.2.1 Safety and Efficacy Endpoints

The secondary efficacy and safety endpoints are as follows:

- The occurrence of sICH [redacted].
- The occurrence of asymptomatic intracranial hemorrhage (ICH) [redacted].
- The occurrence of mortality due to intracerebral or other major bleeding complications [redacted].
- The occurrence of mortality due to any reason [redacted].
- The number and severity of AEs [redacted].
- The number of subjects with AEs [redacted].

- The occurrence of recurrent stroke [redacted].
- Functional outcome
  - The frequency and percentage of subjects with each grade on modified Rankin Scale (mRS) [redacted].
  - The frequency and percentage of subjects [redacted].
- Neurological outcome
  - Absolute change in NIHSS [redacted].
  - The proportion of subjects with NIHSS ≤2 [redacted].

[redacted]

7 INVESTIGATIONAL PLAN

7.1 Description of Overall Study Design and Plan

This is a multicenter, double-blind, single-dose, randomized, and placebo-controlled prospective Phase IIa clinical study, designed to evaluate LT3001 drug product versus placebo/control in subjects with AIS.

There is only one dose of LT3001 drug product [redacted]. The dose is based on the results from nonclinical studies, the FIH study in healthy human volunteers (LT3001-101), and US FDA recommendations. Approximately 24 eligible subjects will be randomized 2:1 to LT3001 drug product or placebo. Each eligible subject will receive a single dose of LT3001 drug product or placebo within 24 hours after stroke symptoms onset. LT3001 drug product or placebo will be administered via a [redacted] IV infusion. The infusion will be stopped if an SAE occurs during infusion.

[redacted]

The participation for each subject is approximately 92 days from the screening visit (Visit 1) to the last visit. The study design is illustrated in Figure 1. The Schedule of Assessments is provided in Section 10.

[redacted]

7.2 Discussion of Study Design

For this first study in subjects with AIS, a single-dose placebo-controlled design is chosen.

Because there is no approved drug treatment for AIS for administration beyond 3 hours of stroke onset in the US and beyond 3 to 4.5 hours of stroke onset in Taiwan, a placebo-controlled study

will be ethically acceptable in order to evaluate the drug effect objectively. Preliminary efficacy will be evaluated by assessing the infarct volume, occurrence of recurrent stroke, functional outcome measured by mRS, and neurological outcome measured by the NIHSS.

The dose and regimen chosen is based on results from the nonclinical studies, FIH healthy volunteer study, and US FDA recommendations.

7.3 End of Study

A subject will have fulfilled the requirements for study completion when the subject has completed all study periods, including the last scheduled follow-up visit as indicated in the Schedule of Assessments (Table 10-1).

The end of the study will be the last subject's last visit.

8 SELECTION OF STUDY POPULATION

Section 7.1 provides information regarding number of subjects planned to be randomized.

8.1 Inclusion Criteria

Individuals must meet all of the following criteria to be included in the study:

1. Subject or subject's legal representative consented to participation by signing the informed consent form (ICF) after receiving full information about the study.
2. Subject is aged 18 to 90 years, inclusive, at the time of Screening [redacted].
3. Subject has a NIHSS of 4 to 30.
4. Subject has a clinical diagnosis of AIS within 24 hours after stroke symptoms onset.
5. [redacted]
6. Subject is able to receive the investigational product within 24 hours after stroke symptoms onset.
7. Subjects are women of childbearing potential (WOCBP) or men whose sexual partners are WOCBP, are able and willing to use at least 1 highly effective method of contraception during the study until 3 months after dosing of investigational product.

8.2 Exclusion Criteria

Individuals meeting any of the following criteria at Screening [redacted] or Baseline are ineligible to participate in this study:

1. Subject has been treated with rtPA and/or endovascular thrombectomy (EVT) during the current AIS.
2. Subject has a pre-stroke disability that requires help for activities of daily living [redacted].
3. Subject has imaging evidence of acute intracranial hemorrhage, intraparenchymal tumor, arteriovenous malformations, other central nervous system lesions that could increase the risk of bleeding, or aneurysm requiring treatment.
4. [redacted]
5. Subject has symptoms of suspected subarachnoid hemorrhage[redacted].
6. Subject has generalized seizure[redacted].
7. Subject has current uncontrolled hypertensio [redacted].
8. Subject has International Normalized Ratio (INR) >1.7, abnormal activated partial thromboplastin time (aPTT) or platelet count <100,000/mm^3.
9. Subject has blood glucose concentration <50 mg/dL or >400 mg/dL.
10. Subject is lactating, pregnant (pregnancy test required for all female subjects), or planning to become pregnant during the study.
11. Subject has received anticoagulants within 48 hours prior to treatment, e.g., direct oral anticoagulants (e.g., dabigatran, rivaroxaban, apixaban, edoxaban), low molecular weight heparin (e.g., enoxaparin), fondaparinux.
12. Subject has received oral dual antiplatelet therapy and glycoprotein (GP) IIb/IIIa inhibitors within 48 hours prior to treatment.
13. Subject has had prior AIS, myocardial infarction, or serious head trauma within 90 days of Screening [redacted].
14. Subject has history of ICH within 90 days of Screening [redacted].
15. Subject has had any major surgery within 90 days of Screening [redacted], e.g., intracranial or intraspinal surgery, coronary artery bypass graft, obstetrical delivery, organ biopsy.
16. Subject with bleeding event within 21 days of Screening[redacted], e.g., gastrointestinal or hemorrhage.

17. Subject has puncture of noncompressible vessels within 7 days of Screening [redacted].
18. Subject has severe hepatic, renal, and/or active infectious disease at Screening [redacted].
19. Subject has participated in another investigational study and received investigational product within 30 days of Screening [redacted] or 5 half-lives (whichever is longer).
20. In the opinion of the Investigator, the subject is not appropriate for the study for any other reason.

8.3 Rescreening

Individuals who sign the ICF to participate in the study but who do not subsequently meet all the requirements as outlined in the inclusion and exclusion criteria and therefore do not enroll (screen failures) may be rescreened if they have another episode of stroke ≥90 days after the previous one.

8.4 Study Withdrawal, Removal, and Replacement of Subjects

If a subject discontinues study treatment and is withdrawn from the study for any reason, the study site must immediately notify the Medical Monitor (see contact details in Section 12.7.3). The date and the reason for study discontinuation must be recorded on the electronic case report form (eCRF). Subjects who discontinue early from the study will be asked to return to the study site within to complete Early Termination assessments as indicated in the Schedule of Assessments (Table 10-1).

In the event that a subject discontinues prematurely from the study because of a treatment-emergent AE (TEAE) or serious TEAE, the TEAE or serious TEAE will be followed up until it resolves (returns to normal or baseline values) or stabilizes, or until it is judged by the Investigator to no longer be clinically significant.

Once a subject is withdrawn from the study, the subject may not re-enter the study.

A subject may voluntarily withdraw or be withdrawn from the study at any time for reasons including, but not limited to, the following:

- unacceptable toxicity or AE.
- subject withdrawal of consent: at any time, a subject's participation in the study may be terminated at his/her request or on the basis of the Investigator's clinical judgment. The reason for subject withdrawal will be noted on the eCRF.
- intercurrent illness: a condition, injury, or disease unrelated to the primary diagnosis that became apparent during treatment and necessitated the subject's termination from the study.
- general or specific changes in the subject's condition that renders him/her ineligible for further treatment according to the inclusion/exclusion criteria.

- subject fails to adhere to the protocol requirements (e.g., drug noncompliance, failure to return for defined number of visits).
- lost to follow-up: the subject stopped coming for visits, and study personnel were unable to contact the subject 3 times.
- pregnancy, as indicated in Section 12.7.5.

Additionally, the Sponsor may stop the study at any time for safety, regulatory, legal, or other reasons aligned with Good Clinical Practice (GCP). This study may be terminated at the discretion of the Sponsor or any regulatory agency. An Investigator may elect to discontinue or stop the study at his or her study site for any reason, including safety or low enrollment.

9 TREATMENTS

9.1 Details of Study Treatments

Eligible subjects will be randomized 2:1 to LT3001 drug product [redacted] and placebo.

LT3001 drug product will be provided [redacted] in glass vials with butyl rubber stoppers and flip-off aluminum crimp seals. Each vial will contain LT3001 drug substance. [redacted]

All drug supplies will be provided by the Sponsor.

9.2 Dosage Schedule

Subjects randomized to LT3001drug product will receive a single dose of LT3001drug product [redacted]. Subjects randomized to placebo will receive placebo [redacted] as well.

9.3 Measures to Minimize Bias: Study Treatment Assignment and Blinding

The study is placebo-controlled to lessen the risk that events due to chance are falsely attributed to LT3001 drug product.

The study is randomized to control for factors known and unknown between the treatment groups.

The study is blinded so that the subjects, site staff administering the study treatment (LT3001 drug product or placebo), and site staff conducting study assessments will not know which treatment a subject receives to allow assessment of the study objectives without bias.

9.3.1 Method of Study Treatment Assignment

Subjects will be randomly assigned to receive LT3001 drug product or placebo in a ratio of 2:1.

At Screening [redacted] will assign a unique subject identification number to the subject known as the Subject Number. This number

will be associated with the subject throughout the study. [redacted]

The subjects will be centrally randomized at a study level. The treatment assignment will be determined by a randomization list prepared by the biostatistics group [redacted]

9.3.2 Blinding

According to the randomization schedule as indicated in the Schedule of Assessments (Table 10-1) and in accordance with the pharmacy manual, the Investigator or designee will obtain the Randomization Number [redacted], and the Investigator or designee at the study site will be responsible to provide the Subject Number, Randomization Number [redacted] to the unblinded pharmacist or designee for the calculation of study treatment dosage. The unblinded pharmacist or designee will further confirm the Subject Number, Randomization Number, and the study treatment group. [redacted] Prepared study treatments will be identical in appearance and labeled in a blinded manner. Information included on the label includes the Protocol Number, Subject Number, Randomization Number, etc. No other study site personnel, subjects, Sponsor personnel, or Sponsor designees will be unblinded to treatment assignment throughout the duration of the study unless unblinding is required. If an Investigator becomes unblinded to a given subject's study treatment, that subject will be discontinued from the study unless there are ethical reasons for that subject not to be discontinued; approval from the Medical Monitor must be obtained in such instances.

The Investigator must make every effort to contact the Medical Monitor prior to unblinding a subject (contact provided in Section 12.7.3). In the rare event that contact with the Medical Monitor is not possible prior to unblinding, the Investigator reserves the right to unblind in a true emergency, where subject safety is at immediate risk. The unblinding and its cause will also be documented in the eCRF [redacted].

9.4 Treatment Accountability and Compliance

The unblinded pharmacist or other designated individual will maintain records of study treatment delivered to the study site, the inventory at the study site, the distribution to and use by each subject, and the return of materials to the Sponsor for storage or disposal. These records should include dates, quantities, batch/serial numbers, retest dates, in-clinic temperature log, and unique code numbers assigned to the product and study subjects.

Investigators will maintain records that adequately document that the subjects were administered the correct study treatment and reconcile the products received from the drug dispensing center. Investigational product will not be returned to the Sponsor until accountability has been fully monitored.

Administration of investigational product will be supervised by study site personnel to ensure compliance.

9.5 Prior and Concomitant Therapy

9.5.1 Prior and Concomitant Medications

Restricted prior therapies are provided in Section 8.2.

All medications and other treatments taken by the subject during the study, including those treatments initiated before the start of the study, must be recorded on the eCRF.

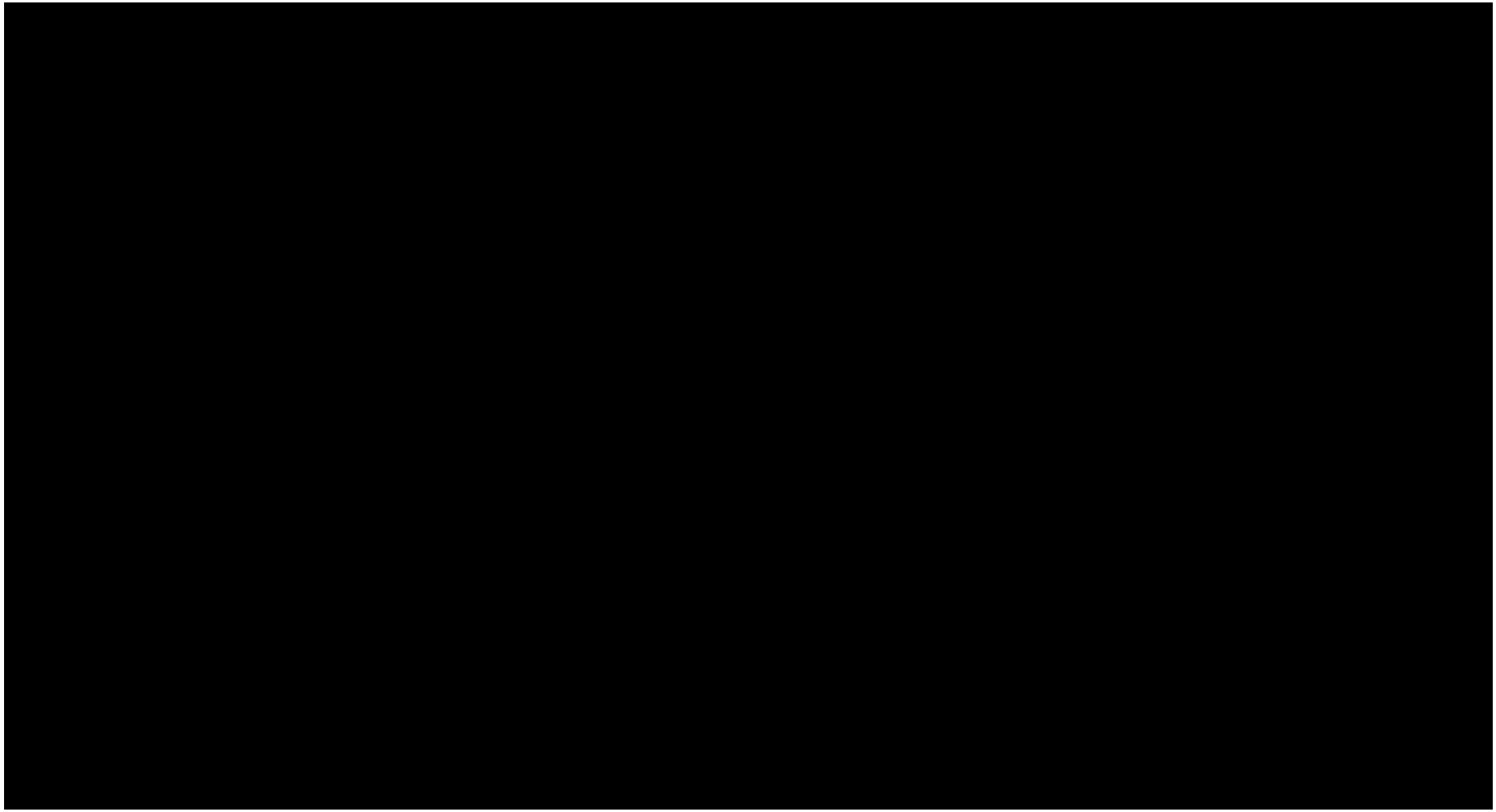
Medications taken by or administered to the subject for the time period before Screening [redacted] will be recorded in the eCRF. After the dosing of investigational product, medication to treat minor treatment-emergent illness(es) is generally permitted. After 24 hours of completion of investigational product infusion, use of antiplatelet agent(s) will be at the discretion of the Investigator. After 24 hours, the following are allowed at the discretion of the Investigator: heparin, non-vitamin K antagonist oral anticoagulant such as dabigatran, rivaroxaban, apixaban, or other factor Xa inhibitors. Low dose heparin or low molecular weight heparin at a preventive dose are allowed from 24 hours after treatment completion and after no intracranial bleeding has been confirmed on 24 hours repeat brain imaging.

Any medication or therapy that is taken by or administered to the subject during the course of the study must be recorded in the eCRF. The entry must include the dose, regimen, route, indication, and dates of use.

10 STUDY PROCEDURES

Table 10-1 outlines the timing of procedures and assessments to be performed throughout the study. Section 12.6 specifies laboratory assessment samples to be obtained. See Sections 11 and 12 for additional details regarding efficacy assessments and safety assessments, respectively.

Table 10-1. Schedule of Assessments



10.1 Informed Consent

Before performing any study-related procedures, the Investigator or designee will obtain the signed ICF from the subject or his/her legally acceptable representative.

In the event that rescreening occurs (see Section 8.3), the individual is required to sign a new ICF and must be assigned a new Subject Number.

10.2 Study Procedures

Assessments and corresponding timings are to be performed as outlined in the Schedule of Assessments (Table 10-1). Section 12.6 specifies laboratory assessment samples to be obtained.

[redacted]

Efficacy assessments are described in Section 11. Efficacy endpoints include occurrences of recurrent stroke, neurological and functional outcomes (via NIHSS and mRS [redacted].

Safety assessments are described in Section 12 and include bleeding assessment (occurrences of sICH and asymptomatic ICH), vital signs, physical and neurological examinations, ECGs, laboratory assessments, and AEs.

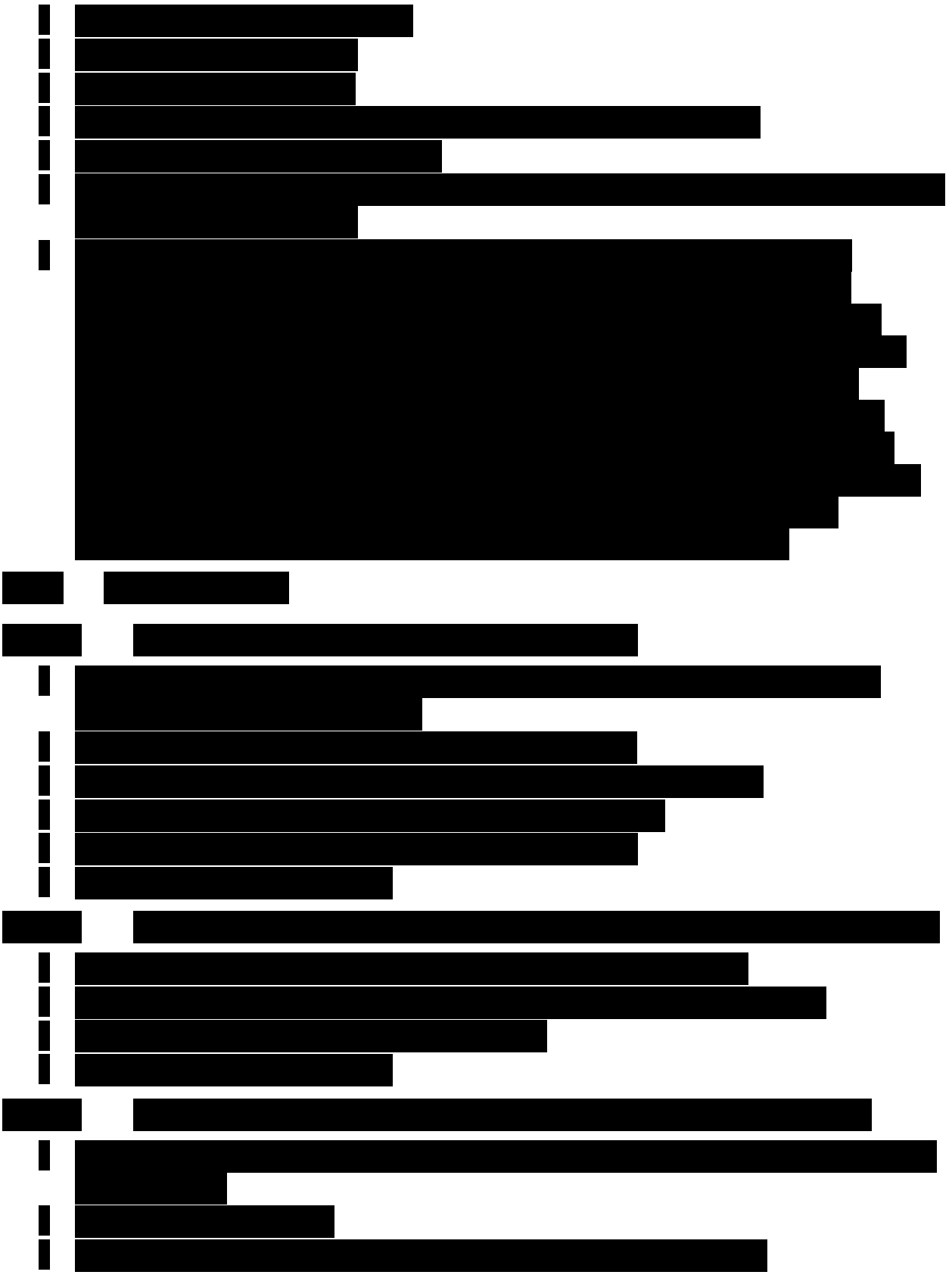
[redacted]

The Investigator may, at his/her discretion, arrange for a subject to have an unscheduled assessment, especially in the case of AEs that require follow-up or are considered by the Investigator to be possibly related to the use of investigational product. The unscheduled visit page in the eCRF must be completed.

Study discontinuation procedures are described in Section 8.4.

Assessments will be done at each visit as detailed in the subsections below.

[redacted]



11 EFFICACY ASSESSMENTS

The Schedule of Assessments (Table 10-1) outlines the efficacy assessments to be performed throughout the study and their timing. Efficacy endpoints include occurrences of recurrent stroke, neurological and functional outcomes (via NIHSS and mRS assessments) [redacted].

11.1 National Institute of Health and Stroke Scale

The NIHSS is a systematic assessment tool that provides a quantitative measure of stroke-related neurologic deficit. It consists of 11 items, each with a score range of 0 to 2-4, with higher scores indicating more deficit/impairment in that specific ability. The total score ranges from 0 (no deficit) to 42 (dead). The score and corresponding description for the NIHSS is provided in Appendix 2.

[redacted].

11.2 Modified Rankin Scale

The mRS measures the degree of disability or dependence in the daily activities of patients who have suffered a stroke. The scale runs from 0 (perfect health without symptoms) to 6 (dead).

[redacted] The score and corresponding description is provided in Appendix 3.

[redacted]

[redacted]

12 SAFETY ASSESSMENTS

Safety assessments (bleeding assessment, vital signs, physical and neurological examinations, ECGs, laboratory assessments, and AEs) are to be performed at protocol-specified visits, as specified in the Schedule of Assessments (Table 10-1).

12.1 Bleeding Assessment

Bleeding assessment will be done by the Investigator or designee and categorized as sICH and asymptomatic ICH. The occurrence of sICH and asymptomatic ICH within 36 hours and 7 days after dosing will be recorded.

12.2 Medical History

Medical history will be recorded at Screening [redacted]. Investigators should document the occurrence, signs, and symptoms of the subject's preexisting conditions, including all prior significant illnesses, up to and including 1 year before Screening [redacted]. Additional preexisting conditions present at the time when informed consent is given and up to the time of the initiation of dosing [redacted] are to be regarded as concomitant illnesses. Medical history will include alcohol consumption and smoking history, if applicable.

Illnesses first occurring or detected during the study and/or worsening of a concomitant illness during the study are to be documented as AEs on the eCRF in accordance with Section 12.7. All changes not present at Baseline or described in the past medical history and identified as clinically noteworthy must be recorded as AEs.

Additionally, demographic data will be collected for all subjects and include date of birth or age according to applicable regulations, gender, and race/ethnicity.

12.3 Vital Signs

Vital signs (body temperature, pulse rate, respiration rate, systolic blood pressure, and diastolic blood pressure) will be measured at the visits indicated in the Schedule of Assessments (Table 10-1). All vital signs will be measured after the subject has been resting in a supine position for at least 5 minutes. Blood pressure measurements are to be taken in the same arm for the duration of the study.

Vital signs measurements will be repeated if clinically significant or machine/equipment errors occur. Out-of-range body temperature, pulse rate, respiratory rate, or blood pressure

measurements will be repeated at the Investigator's or designee's discretion. Any confirmed, clinically significant vital sign measurements must be recorded as AEs.

Body weight (without shoes) will be recorded will be recorded at Screening [redacted] only. For subjects who cannot stand on a scale, bed weight measurement is allowed at the Investigator's or designee's discretion.

12.4 Physical and Neurological Examination

A complete physical examination [redacted] will be performed at Screening [redacted]. Physical examinations will be performed by a physician.

[redacted]

12.5 12-Lead Electrocardiograms

A 12-lead, resting ECG will be obtained at the visits indicated in the Schedule of Assessments (Table 10-1).

At Screening[redacted], the Investigator will examine the ECG traces for signs of cardiac disease that could exclude the subject from the study. An assessment of normal or abnormal will be recorded; if the ECG is considered abnormal, the abnormality will be documented on the eCRF. Electrocardiograms will be repeated if clinically significant abnormalities are observed or artifacts are present at the Investigator's or designee's discretion.

[redacted]

12.6 Laboratory Assessments

Laboratory assessment samples (Table 12-1) are to be obtained at designated visits as detailed in the Schedule of Assessments (Table 10-1).

Table 12-1. Laboratory Assessments

Blood samples will be analyzed at each site. All laboratory reports must be reviewed, signed, and dated by the Investigator or designee. A legible copy of all reports must be filed with both the subject's eCRF and medical record (source document) for that visit. Any laboratory test result considered by the Investigator or designee to be clinically significant should be considered an AE (clinically significant AEs include those that require an intervention). Clinically significant abnormal values occurring during the study will be followed up until repeat test results return to normal, stabilize, or are no longer clinically significant.

12.7 Adverse Events

12.7.1 Adverse Events

An AE is any symptom, physical sign, syndrome, or disease that either emerges during the study or, if present at Screening [redacted], worsens during the study, regardless of the suspected cause of the event. [redacted] Changes in these conditions and new symptoms, physical signs, syndromes, or diseases should be noted on the AE eCRF during the rest of the study. Clinically significant laboratory abnormalities should also be recorded as AEs. Surgical procedures that were planned before the subject enrolled in the study are not considered AEs if the conditions were known before study inclusion; the medical condition should be reported in the subject's medical history. Treatment-emergent AEs (TEAEs) are defined as events with onset dates on or after the start of the investigational product.

Subjects will be instructed to report AEs at each study visit. All AEs are to be followed up until resolution or a stable clinical endpoint is reached.

Each AE is to be documented on the eCRF with reference to date of onset, duration, frequency, severity, relationship to investigational product, action taken with investigational product, treatment of event, and outcome. Furthermore, each AE is to be classified as being serious or nonserious. Changes in AEs and resolution dates are to be documented on the eCRF.

For the purposes of this study, the period of observation for collection of AEs extends from the time the subject gives informed consent until the last follow-up visit. Follow-up of the AE, even after the date of therapy discontinuation, is required if the AE persists until the event resolves or stabilizes at a level acceptable to the Investigator.

When changes in the intensity of an AE occur more frequently than once a day, the maximum intensity for the event should be noted. If the intensity category changes over a number of days, then those changes should be recorded separately (with distinct onset dates).

Specific guidelines for classifying AEs by intensity and relationship to investigational product are given in Table 12-2 and Table 12-3.

Table 12-2. Classification of Adverse Events by Intensity

MILD: An event that is easily tolerated by the subject, causing minimal discomfort, and not interfering with everyday activities.
MODERATE: An event that is sufficiently discomforting to interfere with normal everyday activities.
SEVERE: An event that prevents normal everyday activities.

Table 12-3. Classification of Adverse Events by Relationship to Investigational Product

UNRELATED: This category applies to those AEs that are clearly and incontrovertibly due to extraneous causes (disease, environment, etc).
UNLIKELY: This category applies to those AEs that are judged to be unrelated to the test drug/study procedure but for which no extraneous cause may be found. An AE may be considered unlikely to be related to investigational product /procedure if or when it meets 2 of the following criteria: (1) it does not follow a reasonable temporal sequence from administration of the test drug /study procedure; (2) it could readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; (3) it does not follow a known pattern of response to the test drug/study procedure; or (4) it does not reappear or worsen when the drug/study procedure is readministered.
POSSIBLY: This category applies to those AEs for which a connection with the test drug /study procedure administration appears unlikely but cannot be ruled out with certainty. An AE may be considered possibly related if or when it meets 2 of the following criteria: (1) it follows a reasonable temporal sequence from administration of the drug /study procedure; (2) it could not readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; or (3) it follows a known pattern of response to the test drug /study procedure.
PROBABLY: This category applies to those AEs that the Investigator feels with a high degree of certainty are related to the test drug /study procedure. An AE may be considered probably related if or when it meets 3 of the following criteria: (1) it follows a reasonable temporal sequence from administration of the drug /study procedure; (2) it could not be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; (3) it disappears or decreases on cessation or reduction in dose (note that there are exceptions when an AE does not disappear upon discontinuation of the drug, yet drug-relatedness clearly exists; for example, as in bone marrow depression, fixed drug eruptions, or tardive dyskinesia); or (4) it follows a known pattern of response to the test drug/study procedure.
DEFINITELY: This category applies to those AEs that the Investigator feels are incontrovertibly related to test drug/study procedure. An AE may be assigned an attribution of definitely related if or when it meets all of the following criteria: (1) it follows a reasonable temporal sequence from administration of the drug /study procedure; (2) it could not be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; (3) it disappears or decreases on cessation or reduction in dose and recurs with re-exposure to drug (if rechallenge occurs); and (4) it follows a known pattern of response to the test drug /study procedure.

Abbreviation: AE, adverse event.

12.7.2 Serious Adverse Events

An SAE is any untoward medical occurrence, in the view of either the Investigator or Sponsor, that:

- results in death,
- is life-threatening,
- results in inpatient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity, and/or
- is a congenital anomaly/birth defect.

Other important medical events that may not be immediately life-threatening or result in death or hospitalization, based upon appropriate medical judgment, are considered SAEs if they are thought to jeopardize the subject and/or require medical or surgical intervention to prevent one of the outcomes defining an SAE. Serious AEs are critically important for the identification of significant safety problems; therefore, it is important to take into account both the Investigator's and the Sponsor's assessment. If either the Sponsor or the Investigator believes that an event is serious, the event must be considered serious and evaluated by the Sponsor for expedited reporting.

12.7.3 Serious Adverse Event Reporting

An SAE occurring from the time informed consent is obtained, during the study, or within 3 months of stopping the treatment must be reported to the [redacted] Safety and Pharmacovigilance group and will be communicated to the Sponsor. Any such SAE due to any cause, whether or not related to the investigational product, must be reported within 24 hours of occurrence or when the Investigator becomes aware of the event. Notification can be made using the dedicated fax line or email [redacted] Safety and Pharmacovigilance group:

[redacted]

If the Investigator contacts the [redacted] Safety and Pharmacovigilance group by telephone, then a written report must follow within 24 hours and is to include a full description of the event and sequelae in the format detailed in the SAE reporting form.

The event must also be recorded on the standard AE eCRF. Preliminary reports of SAEs must be followed up by detailed descriptions later on, including clear and anonymized photocopies of hospital case reports, consultant reports, autopsy reports, and other documents when requested and applicable. SAE reports must be made whether or not the Investigator considers the event to be related to the investigational drug.

Appropriate remedial measures should be taken to treat the SAE, and the response should be recorded. Clinical, laboratory, and diagnostic measures should be employed as needed in order to determine the etiology of the problem. The Investigator must report all additional follow-up evaluations to the [redacted] Safety and Pharmacovigilance group within 24 hours of becoming aware of the additional information or as soon as is practicable. All SAEs will be followed up until the Investigator and Sponsor agree the event is satisfactorily resolved.

Any SAE that is not resolved by the end of the study or upon discontinuation of the subject's participation in the study is to be followed up until it either resolves, stabilizes, returns to baseline values (if a baseline value is available), or is shown to not be attributable to the investigational product or procedures.

12.7.4 Suspected Unexpected Serious Adverse Reactions

Adverse events that meet all of the following criteria will be classified as suspected unexpected serious adverse reactions (SUSARs) and reported to the appropriate regulatory authorities in accordance with applicable regulatory requirements for expedited reporting:

- serious
- unexpected (i.e., the event is not consistent with the safety information in the IB)
- there is at least a reasonable possibility that there is a causal relationship between the event and the study treatment

The Investigator will assess whether an event is causally related to study treatment. The Sponsor [redacted] will consider the Investigator's assessment and determine whether the event meets the criteria for being reportable as a 7-day or 15-day safety report. Suspected unexpected serious adverse reactions (SUSARs) that are fatal or life-threatening must be reported to the regulatory authorities and the independent ethics committee (IEC)/institutional review boards (IRBs) (where required) within 7 days after the Sponsor [redacted] has first knowledge of them, with a follow-up report submitted within a further 8 calendar days. Other SUSARs must be reported to the relevant regulatory authorities and the IEC/IRBs within 15 calendar days after the Sponsor [redacted] first has knowledge of them.

The Sponsor [redacted] is responsible for reporting SUSARs and any other events required to be reported in an expedited manner to the regulatory authorities and for informing Investigators of reportable events, in compliance with applicable regulatory requirements within specific timeframes. Investigators will notify the relevant IEC/IRBs of reportable events within the applicable timeframes.

12.7.5 Pregnancy

Women of childbearing potential (WOCBP) must have a negative pregnancy test at Screening [redacted]. Following administration of investigational product, any known cases of pregnancy in female subjects will be reported until the subject completes or withdraws from the study. The pregnancy will be reported immediately by faxing/emailing a completed pregnancy report to the Sponsor (or designee) within 24 hours of knowledge of the event. The pregnancy will not be processed as an SAE; however, the Investigator will follow up with the subject until completion of the pregnancy and must assess the outcome in the shortest possible time but not more than 30 days after completion of the pregnancy. The Investigator should notify the Sponsor (or designee) of the pregnancy outcome by submitting a follow-up pregnancy report. If the outcome of the pregnancy involved spontaneous or therapeutic abortion (any congenital anomaly detected

in an aborted fetus is to be documented), stillbirth, neonatal death, or congenital anomaly, the Investigator will report the event by faxing/emailing a completed pregnancy report form to the Sponsor (or designee) within 24 hours of knowledge of the event.

If the Investigator becomes aware of a pregnancy occurring in the female partner of a male subject participating in the study, the pregnancy should be reported to the Sponsor (or designee) within 24 hours of knowledge of the event. Information regarding the pregnancy must only be submitted after obtaining written consent from the pregnant partner. The Investigator will arrange counseling for the pregnant partner by a specialist to discuss the risks of continuing with the pregnancy and the possible effects on the fetus.

Upon discontinuation from the study, only those procedures that would not expose the subject to undue risk will be performed. The Investigator should also be notified of pregnancy occurring during the study but confirmed after completion of the study. In the event that a subject is subsequently found to be pregnant after inclusion in the study, any pregnancy will be followed to term, and the status of mother and child will be reported to the Sponsor after delivery.

12.7.6 Overdose

The dose level of LT3001 drug product will be calculated by the Investigator or a qualified designee [redacted]. Since drug accumulation is not anticipated due to the short half-life of LT3001 and subjects will only receive LT3001 drug product administered by an Investigator or a qualified designee and under close monitoring, it is anticipated that the risk of overdose or medication error will be low.

Any overdose or medication errors, with or without associated AEs, should be promptly reported by the Investigators or designee to [redacted] Safety and Pharmacovigilance (see contact details in Section 12.7.3). Overdoses and medication errors will be documented as protocol deviations and communicated to the Study Monitor.

No specific therapy for overdose of LT3001 drug product exists. In the event of overdose or medication error, appropriate standard of care therapy for the subject's symptoms and clinical status will be provided.

14 STATISTICAL ANALYSIS

A statistical analysis plan (SAP) will be prepared after the protocol is approved. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives. The SAP will serve as a compliment to the protocol and supersedes it in case of differences.

The statistical evaluation will be performed using SAS® software version 9.4 or higher (SAS Institute, Cary, NC). All data will be listed, and summary tables will be provided. Summary statistics will be presented by treatment group and overall. For continuous variables, data will be summarized with the number of subjects (N), mean, standard deviation, median, minimum, and maximum by treatment group. For categorical variables, data will be tabulated with the number and proportion of subjects for each category by treatment group.

14.1 Determination of Sample Size

Approximately 24 eligible subjects will be randomized 2:1 to LT3001 drug product or placebo. It is planned to have 24 subjects in the Evaluable Population, after which enrollment will stop.

14.2 Analysis Populations

Enrolled Population

The enrolled population will include all individuals who sign the ICF.

Intent-to-Treat (ITT) Population

The ITT population will include all subjects who are randomized, irrespective of any deviation from the protocol or premature discontinuation. The treatment group assignment will be designated according to initial randomization. The ITT population will serve as the primary basis for the analysis of efficacy.

[redacted]

Per-Protocol (PP) Population

The PP population will comprise all ITT subjects who complete study procedures through Day 90 without a major protocol deviation. The PP population will also be used for the analysis of efficacy.

[redacted]

[redacted]

Safety Population

The safety population will include all randomized subjects who receive at least 1 dose of investigational product. The treatment group assignment in this population will be defined by the treatment actually received. This population will be used for the analysis of safety.

14.3 Safety Analysis

14.3.1 Analysis of Primary Safety Endpoint

The frequency and proportion of symptomatic intracranial hemorrhage (sICH) within 36 hours of dosing will be reported by treatment group and overall. Comparisons by treatment group will be made [redacted]

14.3.2 Analysis of Secondary Safety Endpoints

14.3.2.1 Occurrence of sICH [redacted]

The frequency and proportion of sICH [redacted] will be reported by treatment group and overall. Symptomatic ICH will not be imputed for subjects missing either NIHSS score or CT/MRI examination so the denominator will be the number of subjects in whom sICH could be assessed. Comparisons of treatment group will be made [redacted] no formal adjustment for multiple comparisons will be made.

14.3.2.2 Occurrence of Asymptomatic ICH [redacted]

The frequency and proportion of asymptomatic ICH at each time point will be reported by treatment group and overall. Intracranial hemorrhage will not be imputed for subjects missing either NIHSS score or CT/MRI examination at each visit so the denominator will be the number of subjects in whom ICH could be assessed. Comparisons of treatment group will be made [redacted] no formal adjustment for multiple comparisons will be made.

14.3.2.3 Occurrence of Mortality Due to Intracerebral or Other Major Bleeding Complications [redacted]

The frequency and proportion of subjects who have died due to intracerebral or other major bleeding complications at each time point will be reported by treatment group and overall. [redacted]

14.3.2.4 Occurrence of Mortality Due to Any Reason [redacted]

The frequency and proportion of subjects who have died due to any reason will be reported at each time point by treatment group and overall. Comparisons of treatment group will be made [redacted] no formal adjustment for multiple comparisons will be made.

14.3.2.5 Proportion of Subjects With an Increase in the NIHSS of ≥4 Points

The overall proportion of subjects with an increase in the NIHSS of ≥4 points will be presented by treatment group [redacted]

14.3.2.6 Other Safety Analyses

All reported AEs will be coded using the current Medical Dictionary for Regulatory Activities (MedDRA) in place at the time of analysis. The incidence of TEAEs within 90 days after dosing, including severity, will be included in incidence tables. The summary tables will include the number of subjects and the number of events. Percentages will be based on the number of subjects. Events with missing onset dates will be included as treatment-emergent. If a subject experiences more than 1 occurrence of the same AE, the occurrence with the greatest severity and the closest association with the investigational product will be used in the summary tables. Serious AEs and AEs causing discontinuation will be tabulated. All AEs will be listed by subject, along with information regarding onset, duration, relationship and severity to investigational product, action taken with investigational product, treatment of event, and outcome.

Clinical laboratory data, vital signs, and 12-lead ECG will be summarized using descriptive statistics, including mean values and mean change from baseline values, as well as numbers of subjects with values outside limits of the normal range at each time point. For laboratory tests, abnormal values will be flagged in the data listings.

Summary tables will be provided for concomitant medications initiated during the study period.

14.4 Efficacy Analyses

14.4.1 Occurrence of Recurrent Stroke [redacted]

The frequency and proportion of subjects who have a recurrent stroke within 90 days of dosing will be reported by treatment group and overall.

[redacted]

14.4.3 National Institute of Health Stroke Scale

The NIHSS is a standardized method to measure the level of impairment caused by a stroke and was developed by the National Institutes of Health. The NIHSS allows for objective comparison of efficacy across different treatments for stroke, including rehabilitation interventions.

The NIHSS is a brief and reliable stroke deficit assessment scale composed of 11 components and the numbers of grades for each component vary; however, for each component, a score of 0 is defined as normal while higher scores indicate increasing severity of impairment.

[redacted] Data missing on the visit level will not be imputed, and no statistical inferences will be performed.

The proportion of subjects with NIHSS of 0-2 points will be presented by treatment group [redacted]

14.4.4 Modified Rankin Scale

The mRS is a global disability scale that measures the overall independence of stroke patients. The level of disability following a stroke is assessed via a 7-point scale (0-6), where 0 is no limitation or symptom and 6 is death. It is expected that all subjects will have a baseline of 1 (no significant disabilities despite symptoms) up to 5 (severe disability, bedridden, incontinent, and requiring constant nursing care and attention).

For each shift table, missing values will not be included, so the denominator for percentages will be the number of subjects with a mRS score at both Baseline and the visit. No missing values will be imputed and no statistical inference will be performed on the shift tables.

The frequency and percentage of subjects with each grade on the mRS [redacted] will be presented by treatment group.

The frequency and percentage of subjects who achieve a score of 0 to 2 [redacted] will be presented by treatment group. Comparisons by treatment group will be made [redacted]. No formal adjustment for multiple comparisons will be made.

[redacted]

[redacted]

14.6 Interim Analysis

No interim analyses are planned.

[redacted]

[redacted]

15 STUDY MANAGEMENT

15.1 Approval and Consent

15.1.1 Regulatory Guidelines

This study will be conducted in accordance with the accepted version of the Declaration of Helsinki and/or all relevant regulations, as set forth in Parts 50, 56, 312, Subpart D, of Title 21 of the United States Code of Federal Regulations (CFR), in compliance with International Council for Harmonisation (ICH) and GCP guidelines, and according to the appropriate regulatory requirements in the countries where the study is conducted.

15.1.2 Institutional Review Board/Independent Ethics Committee

Conduct of the study must be approved by an appropriately constituted IEC/IRB. Approval is required for the study protocol, protocol amendments (if applicable), IB, ICFs, recruitment material, and subject information sheets and other subject-facing material.

15.1.3 Informed Consent

For each study subject, written informed consent will be obtained before any protocol-related activities. As part of this procedure, the Investigator or designee must explain orally and in writing the nature of the study, its purpose, procedures, expected duration, alternative therapy available, and the benefits and risks involved in study participation. The subject should be informed that he/she may withdraw from the study at any time, and the subject will receive all information that is required by local regulations and guidelines for ICH. The Investigator will provide the Sponsor or its representative with a copy of the IEC-/IRB-approved ICF(s) before the start of the study.

15.2 Data Handling

Any data to be recorded directly on the eCRFs (to be considered as source data) will be identified at the start of the study. Data reported on the eCRF that are derived from source documents should be consistent with the source documents, or the discrepancies must be explained. See also Section 15.3.

Clinical data will be entered by site personnel on eCRFs for transmission to the Sponsor. Data on eCRFs transmitted via the web-based data system must correspond to and be supported by source documentation maintained at the study site, unless the study site makes direct data entry to the databases for which no other original or source documentation is maintained. In such cases, the study site should document which eCRFs are subject to direct data entry and should have in place procedures to obtain and retain copies of the information submitted by direct data entry. All study forms and records transmitted to the Sponsor must only include coded identifiers such that directly identifying personal information is not transmitted. The primary method of data transmittal is via the secure, internet-based EDC system [redacted]. Access to the EDC system is available to only authorized users via the study's internet web site, where a user unique assigned username and password are required for access.

Any changes made to data after collection will be made through the use of the EDC system. Electronic CRFs will be considered complete when all missing and/or incorrect data have been resolved.

15.3 Source Documents

Source documents are considered to be all information in original records and certified copies of original records of clinical findings, observations, data, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. The Investigator will provide direct access to source documents and/or source data in the facilitation of trial-related monitoring, audits, review by IECs/IRBs, and regulatory inspections.

The Investigator/institution should maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial subjects. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, not obscure the original entry, and be explained if necessary.

15.4 Record Retention

Study records and source documents must be preserved for at least 15 years after the completion or discontinuation of/withdrawal from the study, at least 2 years after the drug being studied has received its last approval for sale, or at least 2 years after the drug development has stopped, and in accordance with the applicable local privacy laws, whichever is the longer time period.

The Investigator agrees to comply with all applicable federal, state, and local laws and regulations relating to the privacy of subject health information, including, but not limited to, the Standards for Individually Identifiable Health Information, 45 CFR, Parts 160 and 164 (the Health Insurance Portability Accountability Act of 1996 [HIPAA] Privacy Regulation). The Investigator shall ensure that study subjects authorize the use and disclosure of protected health information in accordance with HIPAA Privacy Regulation and in a form satisfactory to the Sponsor.

15.5 Monitoring

The study will be monitored according to the study's monitoring plan to ensure that it is conducted and documented properly according to the protocol, GCP, and all applicable regulatory requirements.

Monitoring visits (on-site and remote [telephone] or a combination of both) and contacts will be made at appropriate times during the study. The Principal Investigator will assure he/she and adequate site personnel are available throughout the study to collaborate with clinical monitors. Clinical monitors must have direct access to source documentation in order to check the completeness, clarity, and consistency of the data recorded in the eCRFs for each subject.

The Investigator will make available to the clinical monitor all source documents and medical records necessary to review protocol adherence and eCRFs. In addition, the Investigator will work closely with the clinical monitor and, as needed, provide them appropriate evidence that the study is being conducted in accordance with the protocol, applicable regulations, and GCP guidelines.

15.6 Quality Control and Quality Assurance

The Sponsor or its designee will perform the quality assurance and quality control activities of this study; however, responsibility for the accuracy, completeness, security, and reliability of the study data presented to the Sponsor lies with the Investigator generating the data.

The Sponsor will arrange audits as part of the implementation of quality assurance to ensure that the study is being conducted in compliance with the protocol, standard operating procedures, GCP, and all applicable regulatory requirements. Audits will be independent of and separate from the routine monitoring and quality control functions. Quality assurance procedures will be performed at study sites and during data management to assure that safety and efficacy data are adequate and well documented.

15.7 Protocol Amendment and Protocol Deviation

15.7.1 Protocol Amendment

Amendments to the protocol that entail corrections of typographical errors, clarifications of confusing wording, changes in study personnel, and minor modifications that have no effect on the safety of subjects or the conduct of the study will be classed as administrative amendments and will be submitted to the IECs/IRBs for information only. The Sponsor will ensure that acknowledgement is received and filed. Amendments that are classed as substantial amendments must be submitted to the appropriate regulatory authorities and the IECs/IRBs for approval and will not be implemented at sites until such approvals are received other than in the case of an urgent safety measure.

15.7.2 Protocol Deviations

Should a protocol deviation occur, the Sponsor must be informed as soon as possible. Protocol deviations and/or violations and the reasons they occurred will be included in the clinical study report. The Sponsor, or its authorized designee, will report protocol deviations to the IRB/IEC and in accordance with applicable regulatory authority.

15.8 Ethical Considerations

This study will be conducted in accordance with this protocol, the accepted version of the Declaration of Helsinki and/or all relevant federal regulations, as set forth in Parts 50, 56, 312, Subpart D, of Title 21 of the CFR; EU 536/2014, Annex 1, D, 17 (a); and in compliance with GCP guidelines.

Independent ethics committees/IRBs will review and approve this protocol and the ICF. All subjects are required to give written informed consent before participation in the study.

15.9 Financing and Insurance

Before the study commences, the Sponsor (or its designee) and the Investigator (or the institution, as applicable) will agree on costs necessary to perform the study. This agreement will be documented in a financial agreement that will be signed by the Investigator (or the institution signatory) and the Sponsor (or its designee).

The Investigator is required to have adequate current insurance to cover claims for negligence and/or malpractice. The Sponsor will provide no-exclusion insurance coverage for the clinical study as required by national regulations.

15.10 Publication Policy/Disclosure of Data

Both the use of data and the publication policy are detailed within the clinical study agreement. Intellectual property rights (and related matters) generated by the Investigator and others performing the clinical study will be subject to the terms of a clinical study agreement that will be agreed between the institution and the Sponsor or their designee. With respect to such rights, the Sponsor or its designee will solely own all rights and interests in any materials, data, and intellectual property rights developed by Investigators and others performing the clinical study described in this protocol, subject to the terms of any such agreement. In order to facilitate such ownership, Investigators will be required to assign all such inventions either to their institution or directly to the Sponsor or its designee, as will be set forth in the clinical study agreement.

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17 APPENDICES

APPENDIX 1 Contraception Guidelines

APPENDIX 2 National Institute of Health Stroke Scale (Sample)

APPENDIX 3 modified Rankin Scale (Sample)

APPENDIX 1. Contraception Guidelines

Women of childbearing potential (WOCBP) and men whose sexual partners are WOCBP must use at least 1 highly effective method of contraception during the study and for 3 months after dosing of study treatment.

A woman is considered to be a WOCBP (fertile) following menarche and until becoming postmenopausal, unless she is permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

A man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy.

Highly effective methods of contraception are those which have a failure rate of <1% [redacted]

All subjects will be strongly advised that they (or the female partners of male subjects) should not become pregnant while on study treatment or for 3 months after dosing of investigational product. A female subject will be advised that she must report immediately to the study site for pregnancy testing and appropriate management in the event that she may be pregnant.

Reference

1. [HMA] Heads of Medicines Agencies. Clinical Trial Facilitation Group page. Recommendations related to contraception and pregnancy testing in clinical trials. http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf. September 15, 2014. Accessed 12 Mar 2019.

APPENDIX 2. Institute of Health Stroke Scale (Sample)

NIH STROKE SCALE

Patient Identification. ___ - ___ - ___

Pt. Date of Birth ___/___/___

Hospital _____(___ - ___)

Date of Exam ___/___/___

Interval: [ ] Baseline [ ] 2 hours post treatment [ ] 24 hours post onset of symptoms ±20 minutes [ ] 7-10 days
[ ] 3 months [ ] Other _____(___)

Time: ___:___ [ ]am [ ]pm

Person Administering Scale _____

Administer stroke scale items in the order listed. Record performance in each category after each subscale exam. Do not go back and change scores. Follow directions provided for each exam technique. Scores should reflect what the patient does, not what the clinician thinks the patient can do. The clinician should record answers while administering the exam and work quickly. Except where indicated, the patient should not be coached (i.e., repeated requests to patient to make a special effort).

Instructions	Scale Definition	Score
1a. Level of Consciousness: The investigator must choose a response if a full evaluation is prevented by such obstacles as an endotracheal tube, language barrier, orotracheal trauma/bandages. A 3 is scored only if the patient makes no movement (other than reflexive posturing) in response to noxious stimulation.	0 = **Alert;** keenly responsive. 1 = **Not alert**; but arousable by minor stimulation to obey, answer, or respond. 2 = **Not alert**; requires repeated stimulation to attend, or is obtunded and requires strong or painful stimulation to make movements (not stereotyped). 3 = Responds only with reflex motor or autonomic effects or totally unresponsive, flaccid, and areflexic.	____
1b. LOC Questions: The patient is asked the month and his/her age. The answer must be correct - there is no partial credit for being close. Aphasic and stuporous patients who do not comprehend the questions will score 2. Patients unable to speak because of endotracheal intubation, orotracheal trauma, severe dysarthria from any cause, language barrier, or any other problem not secondary to aphasia are given a 1. It is important that only the initial answer be graded and that the examiner not "help" the patient with verbal or non-verbal cues.	0 = **Answers** both questions correctly. 1 = **Answers** one question correctly. 2 = **Answers** neither question correctly.	____
1c. LOC Commands: The patient is asked to open and close the eyes and then to grip and release the non-paretic hand. Substitute another one step command if the hands cannot be used. Credit is given if an unequivocal attempt is made but not completed due to weakness. If the patient does not respond to command, the task should be demonstrated to him or her (pantomime), and the result scored (i.e., follows none, one or two commands). Patients with trauma, amputation, or other physical impediments should be given suitable one-step commands. Only the first attempt is scored.	0 = **Performs** both tasks correctly. 1 = **Performs** one task correctly. 2 = **Performs** neither task correctly.	____
2. Best Gaze: Only horizontal eye movements will be tested. Voluntary or reflexive (oculocephalic) eye movements will be scored, but caloric testing is not done. If the patient has a conjugate deviation of the eyes that can be overcome by voluntary or reflexive activity, the score will be 1. If a patient has an isolated peripheral nerve paresis (CN III, IV or VI), score a 1. Gaze is testable in all aphasic patients. Patients with ocular trauma, bandages, pre-existing blindness, or other disorder of visual acuity or fields should be tested with reflexive movements, and a choice made by the investigator. Establishing eye contact and then moving about the patient from side to side will occasionally clarify the presence of a partial gaze palsy.	0 = **Normal.** 1 = **Partial gaze palsy;** gaze is abnormal in one or both eyes, but forced deviation or total gaze paresis is not present. 2 = **Forced deviation,** or total gaze paresis not overcome by the oculocephalic maneuver.	____

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NIH STROKE SCALE

Patient Identification: ___ ___ - ___ ___ ___ ___ ___ ___

Pt. Date of Birth ___ ___/___ ___/___ ___

Hospital _____(___ ___ - ___ ___)

Date of Exam ___ ___/___ ___/___ ___

Interval: [ ] Baseline [ ] 2 hours post treatment [ ] 24 hours post onset of symptoms ±20 minutes [ ] 7-10 days
[ ] 3 months [ ] Other _____(___ ___)

3. Visual: Visual fields (upper and lower quadrants) are tested by confrontation, using finger counting or visual threat, as appropriate. Patients may be encouraged, but if they look at the side of the moving fingers appropriately, this can be scored as normal. If there is unilateral blindness or enucleation, visual fields in the remaining eye are scored. Score 1 only if a clear-cut asymmetry, including quadrantanopia, is found. If patient is blind from any cause, score 3. Double simultaneous stimulation is performed at this point. If there is extinction, patient receives a 1, and the results are used to respond to item 11.	0 = **No visual loss.** 1 = **Partial hemianopia.** 2 = **Complete hemianopia.** 3 = **Bilateral hemianopia** (blind including cortical blindness).	____
4. Facial Palsy: Ask – or use pantomime to encourage – the patient to show teeth or raise eyebrows and close eyes. Score symmetry of grimace in response to noxious stimuli in the poorly responsive or non-comprehending patient. If facial trauma/bandages, orotracheal tube, tape or other physical barriers obscure the face, these should be removed to the extent possible.	0 = **Normal** symmetrical movements. 1 = **Minor paralysis** (flattened nasolabial fold, asymmetry on smiling). 2 = **Partial paralysis** (total or near-total paralysis of lower face). 3 = **Complete paralysis** of one or both sides (absence of facial movement in the upper and lower face).	____
5. Motor Arm: The limb is placed in the appropriate position: extend the arms (palms down) 90 degrees (if sitting) or 45 degrees (if supine). Drift is scored if the arm falls before 10 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime, but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic arm. Only in the case of amputation or joint fusion at the shoulder, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice.	0 = **No drift;** limb holds 90 (or 45) degrees for full 10 seconds. 1 = **Drift;** limb holds 90 (or 45) degrees, but drifts down before full 10 seconds; does not hit bed or other support. 2 = **Some effort against gravity;** limb cannot get to or maintain (if cued) 90 (or 45) degrees, drifts down to bed, but has some effort against gravity. 3 = **No effort against gravity;** limb falls. 4 = **No movement.** UN = **Amputation** or joint fusion, explain: _____ **5a. Left Arm** **5b. Right Arm**	____ ____
6. Motor Leg: The limb is placed in the appropriate position: hold the leg at 30 degrees (always tested supine). Drift is scored if the leg falls before 5 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime, but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic leg. Only in the case of amputation or joint fusion at the hip, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice.	0 = **No drift;** leg holds 30-degree position for full 5 seconds. 1 = **Drift;** leg falls by the end of the 5-second period but does not hit bed. 2 = **Some effort against gravity;** leg falls to bed by 5 seconds, but has some effort against gravity. 3 = **No effort against gravity;** leg falls to bed immediately. 4 = **No movement.** UN = **Amputation** or joint fusion, explain: _____ **6a. Left Leg** **6b. Right Leg**	____

Rev 10/1/2003

NIH STROKE SCALE

Patient Identification: ___ ___ ___ ___ ___ ___ ___ ___

Pt. Date of Birth ___/___/___

Hospital _____(___ ___ ___ ___)

Date of Exam ___/___/___

Interval: [ ] Baseline [ ] 2 hours post treatment [ ] 24 hours post onset of symptoms ±20 minutes [ ] 7-10 days
[ ] 3 months [ ] Other _____(___ ___)

7. Limb Ataxia: This item is aimed at finding evidence of a unilateral cerebellar lesion. Test with eyes open. In case of visual defect, ensure testing is done in intact visual field. The finger-nose-finger and heel-shin tests are performed on both sides, and ataxia is scored only if present out of proportion to weakness. Ataxia is absent in the patient who cannot understand or is paralyzed. Only in the case of amputation or joint fusion, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice. In case of blindness, test by having the patient touch nose from extended arm position.	0 = **Absent.** 1 = **Present in one limb.** 2 = **Present in two limbs.** UN = **Amputation** or joint fusion, explain: _____	____
8. Sensory: Sensation or grimace to pinprick when tested, or withdrawal from noxious stimulus in the obtunded or aphasic patient. Only sensory loss attributed to stroke is scored as abnormal and the examiner should test as many body areas (arms (not hands), legs, trunk, face) as needed to accurately check for hemisensory loss. A score of 2, "severe or total sensory loss," should only be given when a severe or total loss of sensation can be clearly demonstrated. Stuporous and aphasic patients will, therefore, probably score 1 or 0. The patient with brainstem stroke who has bilateral loss of sensation is scored 2. If the patient does not respond and is quadriplegic, score 2. Patients in a coma (item 1a=3) are automatically given a 2 on this item.	0 = **Normal;** no sensory loss. 1 = **Mild-to-moderate sensory loss;** patient feels pinprick is less sharp or is dull on the affected side; or there is a loss of superficial pain with pinprick, but patient is aware of being touched. 2 = **Severe to total sensory loss;** patient is not aware of being touched in the face, arm, and leg.	____
9. Best Language: A great deal of information about comprehension will be obtained during the preceding sections of the examination. For this scale item, the patient is asked to describe what is happening in the attached picture, to name the items on the attached naming sheet, and to read from the attached list of sentences. Comprehension is judged from responses here, as well as to all of the commands in the preceding general neurological exam. If visual loss interferes with the tests, ask the patient to identify objects placed in the hand, repeat, and produce speech. The intubated patient should be asked to write. The patient in a coma (item 1a=3) will automatically score 3 on this item. The examiner must choose a score for the patient with stupor or limited cooperation, but a score of 3 should be used only if the patient is mute and follows no one-step commands.	0 = **No aphasia;** normal. 1 = **Mild-to-moderate aphasia;** some obvious loss of fluency or facility of comprehension, without significant limitation on ideas expressed or form of expression. Reduction of speech and/or comprehension, however, makes conversation about provided materials difficult or impossible. For example, in conversation about provided materials, examiner can identify picture or naming card content from patient's response. 2 = **Severe aphasia;** all communication is through fragmentary expression; great need for inference, questioning, and guessing by the listener. Range of information that can be exchanged is limited; listener carries burden of communication. Examiner cannot identify materials provided from patient response. 3 = **Mute, global aphasia;** no usable speech or auditory comprehension.	____
10. Dysarthria: If patient is thought to be normal, an adequate sample of speech must be obtained by asking patient to read or repeat words from the attached list. If the patient has severe aphasia, the clarity of articulation of spontaneous speech can be rated. Only if the patient is intubated or has other physical barriers to producing speech, the examiner should record the score as untestable (UN), and clearly write an explanation for this choice. Do not tell the patient why he or she is being tested.	0 = **Normal.** 1 = **Mild-to-moderate dysarthria;** patient slurs at least some words and, at worst, can be understood with some difficulty. 2 = **Severe dysarthria;** patient's speech is so slurred as to be unintelligible in the absence of or out of proportion to any dysphasia, or is mute/anarthric. UN = **Intubated** or other physical barrier, explain: _____	____

Rev 10/1/2003

NIH STROKE SCALE

Patient Identification. _____-___-_____-___-_____

Pt. Date of Birth ____/___ ___/____

Hospital _____(____-___)

Date of Exam ____/___ ___/____

Interval: [ ] Baseline [ ] 2 hours post treatment [ ] 24 hours post onset of symptoms ±20 minutes [ ] 7-10 days
[ ] 3 months [ ] Other _____(____)

11. Extinction and Inattention (formerly Neglect): Sufficient information to identify neglect may be obtained during the prior testing. If the patient has a severe visual loss preventing visual double simultaneous stimulation, and the cutaneous stimuli are normal, the score is normal. If the patient has aphasia but does appear to attend to both sides, the score is normal. The presence of visual spatial neglect or anosagnosia may also be taken as evidence of abnormality. Since the abnormality is scored only if present, the item is never untestable.	0 = **No abnormality.** 1 = **Visual, tactile, auditory, spatial, or personal inattention** or extinction to bilateral simultaneous stimulation in one of the sensory modalities. 2 = **Profound hemi-inattention or extinction to more than one modality;** does not recognize own hand or orients to only one side of space.	____

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APPENDIX 3. Modified Rankin Scale (Sample)

Score	Description
0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability; requiring some help, but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention
6	Dead